Pharmacokinetic evaluation of linezolid in burn patients

L. Ben Gharsallah (1); A Mokline (1); I Rahmani (1); E. Gaies (2); B. Gasri (1); R Hammouda (1); S Tlaili (1); T. Sameh (2); A. Klouz (2); AA Messadi (1)

(1) Intensive Burn Care Department, Burn and Trauma Center – Tunis, Tunisia.
(2) Laboratory of pharmacology, Charles Nicole University Hospital– Tunis, Tunisia

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NO CONFLICT OF INTEREST

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INTRODUCTION

- **Patients with major burns experience pathological changes which have been shown to influence the pharmacokinetics of antibiotics.**
- **Subsequently it has been demonstrated that conventional doses of some antibiotics given to patients with major burns may result in sub-therapeutic serum concentrations .**

INTRODUCTION

Linezolid is an antibiotic with time-dependent activity, PK/PD considerations are important in optimizing both antibacterial activity and development of resistance to linezolid.

Because of its intrinsic chemico-physical and pharmacokinetic characteristics, it is assumed that adequate serum linezolid concentrations will be achieved most of the time when using the recommended dose of 600 mg every 12 hours.

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Zoller *et al. Critical Care* 2014, **18**:R148
http://ccforum.com/content/18/4/R148

CRITICAL CARE

RESEARCH Open Access

Variability of linezolid concentrations after standard dosing in critically ill patients: a prospective observational study

Michael Zoller[1], Barbara Maier[2], Cyrill Hornuss[1], Christina Neugebauer[1], Gundula Döbbeler[1], Dorothea Nagel[2], Lesca Miriam Holdt[2], Mathias Bruegel[2], Thomas Weig[1], Béatrice Grabein[3], Lorenz Frey[1], Daniel Teupser[2], Michael Vogeser[2] and Johannes Zander[2*]

Conclusions: A high variability of linezolid serum concentrations with a substantial percentage of potentially subtherapeutic levels was observed in intensive care patients. The findings suggest that therapeutic drug monitoring of linezolid might be helpful for adequate dosing of linezolid in critically ill patients.

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ANTIMICROBIAL AGENTS AND CHEMOTHERAPY, Apr. 2007, p. 1287–1292 Vol. 51, No. 4
0066-4804/07/$08.00+0 doi:10.1128/AAC.01194-06

Pharmacokinetic/Pharmacodynamic Factors Influencing Emergence of Resistance to Linezolid in an In Vitro Model[▽]

Lauren M. Boak, Jian Li, Craig R. Rayner,† and Roger L. Nation*

It is clear that if Linezolid is used in thermal patients as a 600 mg intravenous twice a day, blood concentrations may be relatively low and risk of emergence of resistance to linezolid increased indicating that higher doses will be needed

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Pathologie Biologie 58 (2010) e27–e31

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Article original

Pharmacocinétique du linézolide chez des patients souffrant de brûlures sévères☆

Pharmacokinetic evaluation of linezolid in patients with major thermal injuries☆

R. Le Floch [a,*], J.-F. Arnould [a], C. Vinsonneau [b], L. Hovsepian [c], J. Stephanazzi [b], P. Bret [d], G. Birraux [d], A.M. Lovering [e]

[a] *Centre de traitement des brûlés, CHU de Nantes, 44093 Nantes cedex 1, France*
[b] *Service des brûlés, hôpital Cochin, 27, rue du Faubourg-St-Jacques, 75679 Paris, France*
[c] *SGS, 3–5, rue Eugène-Million, 75015 Paris, France*
[d] *Pfizer®, 23–25, avenue du Dr-Lannelongue, 75668 Paris cedex 14, France*
[e] *Bristol Centre for Antimicrobial Research and Evaluation, North Bristol NHS Trust, BS10 5NB Bristol, Royaume-Uni*

Methods: In an open-label, multicentre design with two parallel groups, a group of patients with major thermal injuries (>20% body area) and a group of age-, sex- and weight-matched healthy volunteers, subjects received a single 600 mg intravenous dose of linezolid. Serial blood and urine collections were made and the concentrations of linezolid in these samples were determined by HPLC. Non-compartmental analyses were used to describe the pharmacokinetic disposition of linezolid.

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H4: ***2.5mg/l***

H12: ***0.2mg/l***

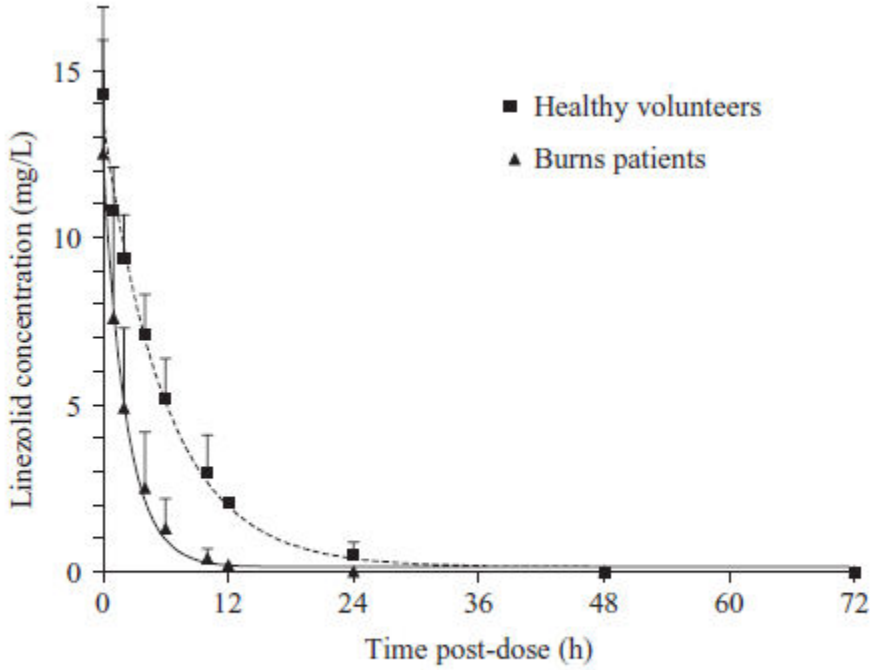

Figure 1. Mean (±SD) plot of linezolid concentration in plasma against time by group.

available in other populations with increased linezolid clearance, increasing the dosing frequency to a three times a day administration of 600 mg seems logical. However, the number of patients in the study was modest and the changes proposed to

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AIM OF STUDY

the pharmacokinetics of linezolid after 3 doses administration of 600mg in major burn-injured patients

The thresholds for potential therapeutic efficacy were defined as

Cmin >2 mg/L and/or AUC24 > 200 mg*h/L.

AUC24/MIC- > 80 to 120

fT>MIC > 85% interval during which antibiotic concentration remain > the MIC

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METHODOLOGY

Prospective study performed in a 20-bed adult burn unit in a university hospital in Tunisia.

***Inclusion criteria*:**

- **Patients with documented and/or suspected MDR Gram-positive**

- **TBSA ≥ 20%**

***Exclusion criteria*:**

- **Age < 18 years**
- **Pregnancy.**

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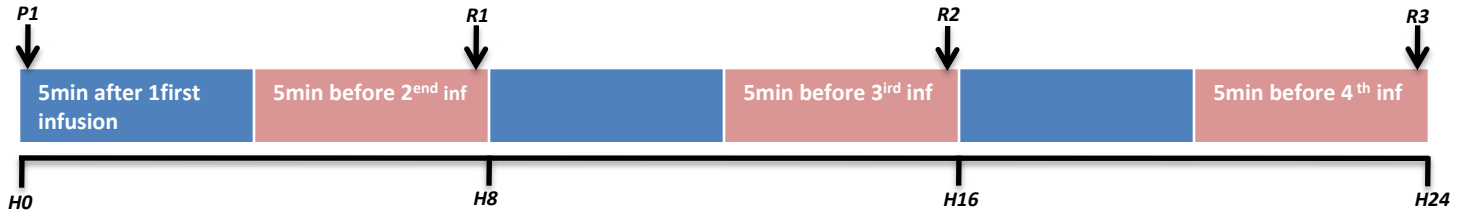
METHODOLOGY

- **Enrolled patients received linezolid as a *3 intravenous* doses: *600 mg* every *8 hours in* a *1 h infusion*.**

- **Blood samples, for pharmacokinetic analysis, were taken 5 min after the end of the infusion, 5min before the second and the third dose and 5 min before the dose of the day after.**



- **To assess linezolid serum level, 4mL of blood was drawn from an arterial line, centrifuged and then conserved at−80 ◦C until analysed.**

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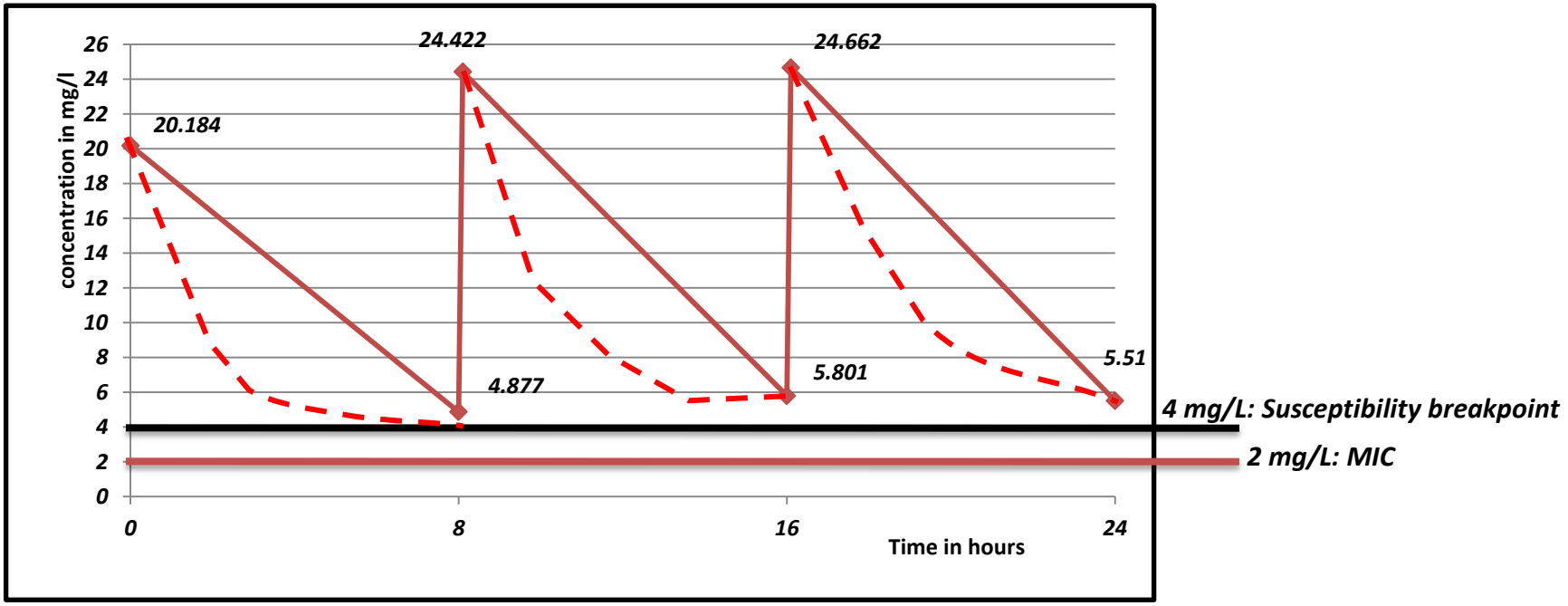
RESULTS

10 septic burn patients were considered eligible for the study.

Characteristics of patients

	N = 10
Sex	8H/2F
Age (years)	39 ± 22
TBSA (%)	30 ± 11
Weight (kg)	68 ± 11
Créatinine (µmol/l)	73 ± 38
Platelet count (mean)	276 ± 176

RESULTS



Mean plasma concentrations of linezolid in all patients

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Linezolid pharmacokinetic parameters of all patients

Patient No.	$AUC_{0\text{-}24h}$ (mg/h/l)	AUC/MIC(2 mg/L)	Cmin (mg/L)
M1	*324*	*162*	*6.11*
M2	*263.07*	*131.53*	*6.21*
M3	*257.58*	*128.79*	*6.04*
M4	*173.28*	*86.64*	*2.11*
M5	*179.52*	*89.625*	*3.05*
M6	*198*	*99*	*6.39*
M7	*107.49*	*53.745*	*1.2*
M8	*488.94*	*244.47*	*6.19*
M9	*387.9*	*193.95*	*8.31*
M10	*151.08*	*75.54*	*2.84*
Mean	**253.05 ± 118.04**	**126.529**	**4.84 ± 2.33**

- **inter-patient variability was observed: The AUC_{24}-values ranged from *107.49* to *488.94* mg/h/L (median 253.05 mg/h/L)**
- **The high inter-patient variability was also observed for single Cmin-values (range from 1.2 to 8.31 mg/L, median 4.84 ± 2.33 mg/L).**

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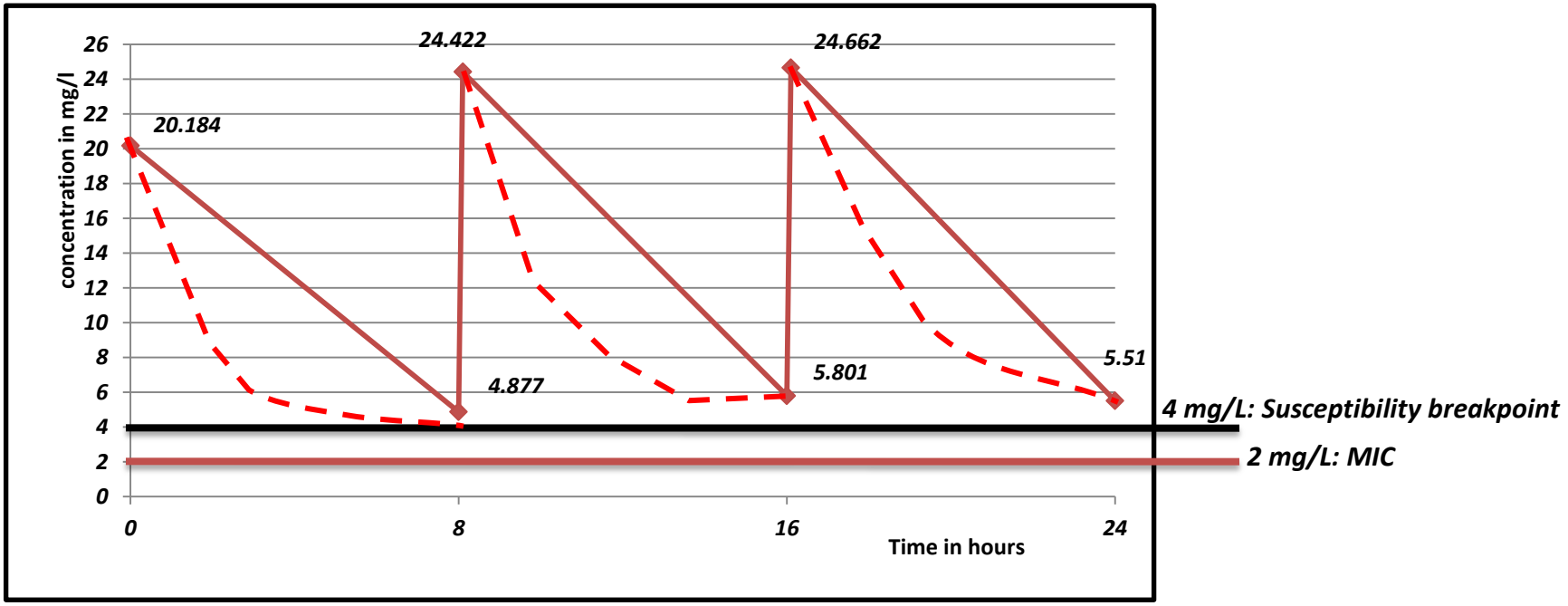
RESULTS



- **fT>MIC > 85%**
- **Time interval during which antibiotic concentration remain > the MIC for 100%.**

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CONCLUSIONS

- Linezolid administration in major burn patients at the dose of 600 mg three times a day allows to reach the thresholds for therapeutic efficacy.

- Improve clinical outcome and minimize the emergence of antibiotic resistance

- the use of therapeutic drug monitoring (TDM) in attempt to optimize the exposure of antibiotics is essentiel particularly in Burn patient.

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THANK YOU